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Appendix A

TITLE (as amended)

USSN09/299,139  
Docket No. A013

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USE OF LYMPHOTOXIN-BETA RECEPTOR BLOCKING AGENTS FOR THE  
TREATMENT OF ANTIBODY MEDIATED IMMUNOLOGICAL DISEASES

SPECIFICATION (As amended)

On page 1, above the Technical Field of the Invention please insert the following continuing data.

Related Applications:

D1  
This is a continuation application under 35 U.S.C. section 365(c) of PCT/US97/19436, filed October 24, 1997, which is a continuation-in-part application of U.S.S.N. 60/029,060 filed on October 25, 1996. The entire disclosures of the aforesaid patent applications are incorporated herein by reference.

On page 55, please replace lines 5-23 with the following:

D2  
The therapeutic methods of the invention involve selectively inhibiting responses that are dependent in whole or in part on the LT- $\beta$  pathway. The particular therapeutic uses of the claimed invention depend upon the relevant etiological mechanism of either the process to be inhibited, or the medically desirable process to be promoted, as will be apparent to those of skill in the art. Thus, the methods of the invention involve, in various embodiments, administering a therapeutically effective amount of a blocking agent of the LT- $\beta$ -R, or LT- $\beta$ . The protein used in these methods may be either full length proteins, fragments of the protein, or fusion fragments. In other embodiments, the methods involve the administration of a soluble fragment, such as a soluble lymphotoxin- $\beta$  receptor. In other preferred embodiments, the claimed invention relates to the administration of antibodies against the LT- $\beta$ -R or LT- $\beta$ . The blocking agents of the invention may be administered concurrently with a therapeutically effective amount of a second compound which exerts a medically desirable effect.

On page 56 please replace lines 1-7 with the following:

D3  
Compositions of the invention may be formulated according to standard practice, such as prepared in a carrier vehicle. The term pharmaceutically acceptable carrier refers to one or more organic or inorganic ingredients, natural or synthetic, which may facilitate the administration of the blocking agents of the invention to a patient. Suitable carriers are known to those of ordinary skill in the art.

On page 56 please replace lines 8-18 with the following:

D4  
Any of the compositions of the invention may be administered in any manner which is medically acceptable. This may include injections, by parenteral routes, such as intravenous, intravascular, intra-arterial, subcutaneous, intramuscular, intratumor, intraperitoneal, intraentricular, intraepidural, or others, as well as oral, nasal, ophthalmic, rectal or topical. Sustained release administration is also specifically included in the invention, by means such as depot injections or implants. Localized delivery may also be desirable. Modes of administration are easily defined by those skilled in the art.

On page 56 please replace lines 19-30 with the following:

D5  
The blocking agents of the LT pathway which are useful in the claimed invention are intended to include functional derivatives of the soluble LT- $\beta$ -R and antibodies claimed herein. Functional derivatives include fragments, variants, analogs or chemical derivatives of a molecule. A fragment of a molecule, such as any of the antigens of the present invention is meant to refer to any polypeptide subset of the molecule. A variant of such molecule is meant to refer to a naturally occurring molecule substantially similar to either the entire molecule, or a fragment thereof. An analog of the molecule refers to a non-natural molecule substantially similar to either the entire molecule or a fragment thereof.

On page 56-57 please replace lines 31-40 with the following:

D6  
Variants of the blocking agents of the invention differ from naturally occurring agents in amino acid sequence, or in ways that do not involve sequence, or both. Variants in amino acid sequence are produced when one or more amino acids in the naturally occurring molecules is substituted with a different natural amino acid, an amino acid derivative, or a non-native amino acid. Particularly preferred variants include the naturally occurring proteins, or biologically active fragments of the naturally occurring proteins, whose sequences differ from the wild type sequence by one or more conservative amino acid substitutions. Such substitutions are well known by those skilled in the art, and typically have a minimal influence on the secondary structure and hydrophobic nature of the blocking agent.

On page 57 please replace lines 11-24 with the following:

D7  
In other embodiments, variants with amino acid substitutions which are less conservative may also result in desired derivatives, e.g., by causing changes in charge, conformation and other biological properties. Such substitutions would include for example, substitution of hydrophilic residues for hydrophobic residues, substitution of a cysteine or a proline for another residue, substitution of a residue having a small side chain for a residue having a bulky side chain, or substitution of a residue having a net positive charge for a residue having a net negative charge. When the result of a given substitution cannot be predicted with certainty, the derivatives may be readily assayed according to the methods disclosed herein to determine the presence or absence of the desired characteristics.

On page 57-58 please replace lines 25-4 with the following:

D8  
Variants within the scope of the invention include proteins and peptides with amino acid sequences having at least eighty percent homology with the blocking agents of the invention. More preferably the sequence homology is at least ninety percent, or at least ninety-five percent. For the purposes of determining homology the length of comparison sequences will generally be at least 8 amino acid residues, usually at least 20 amino acid residues. Variants within the scope of the invention also include any blocking agent which 1) has an amino acid sequence which is at least forty percent homologous to the sequence of the blocking agent, and also which, 2) after being placed in an optimal alignment with the sequence of the blocking agent of the invention, has at least 80 % of its cystein residues aligned with the cysteins of the blocking agent of the invention.

CLAIMS (as amended)

D9 51. A method for inhibiting a humoral immune response in an animal comprising administering a pharmaceutical composition which comprises a therapeutically effective amount of a soluble lymphotoxin- $\beta$  receptor.

D10 61. A method for inhibiting a humoral immune response in an animal comprising administering a pharmaceutical composition which comprises a therapeutically effective amount of an antibody directed against LT- $\beta$  receptor.

D11 65. A method for inhibiting a humoral immune response in an animal comprising administering a pharmaceutical composition which comprises a therapeutically effective amount of an antibody directed against surface LT ligand.

D12 84. A method for disrupting the association of immune complexes and B cell follicles in a patient comprising administering an amount of a soluble lymphotoxin- $\beta$  receptor to said patient.

D13 91. A method for disrupting the association of immune complexes and B cell follicles in a patient comprising administering an amount of an antibody directed against LT- $\beta$  receptor to said patient.

D14 94. A method for disrupting the association of immune complexes and B cell follicles in a patient comprising administering an amount of an antibody directed against surface LT ligand.